Review

Spectrum of Neurologic Complications in Chronic Lymphocytic Leukemia

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Abstract

Neurologic disease is believed to be an unusual complication during the course of chronic lymphocytic leukemia. Nevertheless, it has already been proven in autopsy series that the incidence of occult nervous system infiltration is much higher than was previously expected. The advent of more potent drugs to treat this lymphoproliferative disorder has brought a new hope for a possible cure in the future. However, an appropriate systemic treatment for central nervous system infiltration of this disease is still lacking. Also, due to the potent immunosuppressive properties of the agents used in the up-front treatment, for example, the purine nucleoside analogues, we have witnessed an increase in the incidence of opportunistic infections, with progressive multifocal leukoencephalopathy being one of the most serious. The goal of this review is to summarize the spectrum of neurologic derangements linked to chronic lymphocytic leukemia and to raise clinicians' awareness to recognize the possibility of such associations.

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Introduction

Chronic lymphocytic leukemia (CLL), the most common leukemia that occurs in adulthood, is considered an indolent malignancy of the lymphoid tissue characterized by the proliferation and accumulation of monoclonal, B-type, small, mature-appearing lymphocytes in the blood, bone marrow, and lymphoid tissues. The median age of patients at diagnosis is 65 years, with only 10% to 15% <50 years of age. Men are more affected than women. The course of the disease is variable. That is, most patients with CLL have a normal life span, whereas a subgroup with a more aggressive disease may have a shorter survival after diagnosis.[1] CLL frequently is accompanied by a multitude of immune abnormalities. Defects in both cell-mediated (quantitative and functional B lymphocyte, T cell, natural killer (NK) cells, neutrophils, and the monocyte and/or macrophage abnormalities) and humoral-mediated immunity (low gamma globulin levels) together are responsible for the many disease-specific complications of CLL.[2,3] The central nervous system (CNS) and peripheral nervous system (PNS) are potential targets for CLL-related complications, which are at serious risk of being neglected because it is generally assumed that CLL neurologic complication rates are low.[4] In addition to this belief, clinicians may not be sufficiently aware and prepared to establish an association between the neurologic symptoms and the CLL disease itself, and lose time in search of other etiologies and risk letting the disease reach an irreversible situation.

This review discusses, and also constitutes a reminder of, the vast spectrum of CLL neurologic complications that include not just direct brain, meninges, and root plexus infiltration by the neoplastic cells but also opportunistic infections and secondary brain malignancies due to impaired immunity, CLL therapy-related neurotoxicity, and other lesser well-known but potential neurologic issues, such as metabolic encephalopathies and paraneoplastic neurologic syndromes (Table 1).

Methods

In this narrative literature review, a search strategy that incorporated PubMed-Medline search engines and used the keywords chronic lymphocytic leukemia/leukaemia, small lymphocytic lymphoma, Richter syndrome, central nervous system, meningitis, encephalitis, cerebrospinal fluid, brain tumor, hypophysis/hypothalamus, optic nerve, retina, infection, hemorrhage/haemorrhage, drugs, treatment, chlorambucil, fludarabine, rituximab, neurotoxicity, progressive multifocal leukoencephalopathy, peripheral nervous system, autoimmune neuropathies, vitamin, hypercalcemia, hyponatremia, paraneoplastic neurological syndrome in various combinations was used, and articles were evaluated on an individual basis. The search strategy was not limited by year of publication, and no language restrictions were applied. The search included all research document types, including journal ar-

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Table 1 Overview of the Spectrum of Neurologic Complication in Chronic Lymphocytic Leukemia

Central Nervous System	Etiology
Parenchymal	Leukemic
	Tumor
	Infectious
	Iatrogenic
	Hemorrhagic
	Metabolic
Meningeal	Leukemic
	Infectious
	Hemorrhagic
Epidural	Leukemic
Optic Nerve	Leukemic
	Infectious
	Iatrogenic
Peripheral Nervous System	Leukemic
	Autoimmune
	Iatrogenic

ticles (letters to the editor, case reports, case series, original research reports, reviews), abstracts, and any pertinent document found on the Internet. A review of the reference section of all articles retrieved from the PubMed-Medline database was done to search for any additional relevant articles that could have been overlooked by the electronic search. The articles were selected if they met the criteria of direct or indirect neurologic involvement by CLL and/or small lymphocytic lymphoma and Richter syndrome (RS) transformation.

CLL and CNS Disease

Knowing that CLL is the most common lymphoproliferative disorder in the Western world, with an annual estimated frequency of 3 per 100,000 and that <100 cases of CNS involvement had been reported antemortem in the past 35 years, one at first may be led to believe that CNS invasion is an uncommon event. (Tables 2, 3).[5-71] This is not entirely true for several reasons. First, CNS involvement by CLL is often underdiagnosed and underreported because the neurologic manifestations are nonspecific, and the clinicians may not be sufficiently aware of the possible association between these 2 entities. Second, asymptomatic CNS disease is more prevalent. The postmortem studies confirm this observation: 1 autopsy series detected CNS infiltration in 10 of 14 advanced stage CLL cases, although none of these patients had any neurologic symptoms.[68] In another series of 100 consecutive patients, 16 of whom had CLL, it was found that up to 50% had the silent CNS disease.[69] In a third autopsy series, the reported brain or spinal cord tumor CLL involvement ranged from 17% to 71% of the cases.[70] Also, in a fourth study, which included 109 patients with CLL diagnosed between 1958 and 1982, the percentages of CNS involvement of the brain, dura mater, and leptomeningeal were 7%, 21%, and 8%, respectively.[71] These findings suggest that CLL infiltration in the CNS happens at a much higher rate than was expected. Third, clinical overt neurologic manifestations generally occur in more advanced disease stages or during transformation to RS, although many cases also are diagnosed in the early Rai 0-I stage. There are even situations in which the neurologic symptoms represent the inaugural manifestation of CLL, creating great difficulties to establish, at first, a causal relationship between the hematologic malignancy and the neurologic symptoms. Taken altogether, CNS involvement by CLL is not as rare as it seems to be.

CLL and Meningoencephalitis

Considering only brain parenchyma and/or meningeal infiltration and spinal cord compression by CLL, 67 cases have been described so far,[5-71] a number that is much higher than the previous reports.[34,56,64] The retina and optic nerve, which also belong to the spectrum of CNS involvement by CLL, will be discussed in a separate section, as well as RS of the CNS. In CLL meningoencephalitis, men are affected twice as much as women, and the median age at diagnosis is 64 years. CLL presentation as small lymphocytic lymphoma (SLL) was observed in 4 patients.[38,46,59,63] The distribution according to the Rai staging system was the following: early-stage disease Rai 0-I (n = 30), intermediate stage Rai II (n = 18), and advanced stage Rai III-IV (n = 19). CNS plus systemic disease is the rule, but isolate CNS involvement alone can sometimes occur.[7,32,57,61] Time from CLL diagnosis until CNS documentation of disease ranged from 0 days to 15 years (median, 4.5 years). It is curious to note that 12 cases of brain and/or meningeal infiltration presented as the initial manifestation of diagnosis of CLL (including 2 dura and/or brain SLL, and 3 pituitary and/or hypothalamus CLL).[19,37-40,45,48-50,57,61,63]

There appears to be no correlation between CNS involvement and disease stage in CLL, duration of CLL, sex, age, immunologic phenotype, or peripheral leukocyte count.[70] However, it was suggested that progression to RS seems to predispose to the meningeal invasion.[42] The spectrum of neurologic manifestations is heterogeneous, including headache, cranial nerve palsies (the optic nerve is affected in about a fourth of cases), cerebellar signs, paresis (mainly lower limbs), and visual abnormalities. Paraplegia due to complete cord compression was documented in only 4 instances and carries a very bad prognosis,[7,16,20,36] except in 1 patient in whom prompt decompression surgery plus irradiation and systemic chemotherapy were life saving.[36] Current neuroimaging techniques have low sensitivity for CLL infiltration[49,52,64] because negative or nonspecific results (brain SLL can even be confused with meningioma)[63] are the rule, and only 4 cases showed a brain mass on computed tomography and/or magnetic resonance without infiltration in the cerebrospinal fluid (CSF).[50,61,62,65]

The definitive diagnosis usually is made by CSF analysis. Cytomorphology coupled with immunophenotyping raise the probability of detecting the monoclonal B cells.[49,56] In 2 instances, the use of the polymerase chain reaction (PCR) method that selectively amplified the highly variable and clone-specific CDR3 region of the locus encoding the immunoglobulin heavy chain in DNA obtained from both CSF and peripheral blood cells allowed to the establishment of the suspected diagnosis when both cytology and flow cytometry failed to clarify the clinical suspicion of leptomeningeal disease.[35,40] Notwithstanding, there are cases in which CSF was negative for the

Table 2 Clinical Characteristics, Type of Neurologic Involvement, and Symptoms of the Patients With Documented CNS Involvement by CLL and/or SLL

Study	Sex/Age	Disease	Rai Stage	Sys D	CNS Site	Time to CNS Disease	Clinical Manifestations
Amiel and Droz,[5] 1976	M/69	CLL	0	Y	LM	NA	Headache, ataxia, deafness, cranial nerve palsies
Nemoto et al,[6] 1978	M/33	CLL	II	N	P	NA	Visual loss
Getaz and Miller,[7] 1979	F/65	CLL	IV	Y	SC	NA	Leg weakness
Liepman andVotaw,[8] 1981	F/68	CLL	IV	Y	LM	NA	Cranial nerve palsies
	M/58	CLL	IV	Y	LM	36 mo	Lethargy
Korsager et al,[9] 1982	M/64	CLL	II	Y	LM	NA	Dementia
	M/58	CLL	II	Y	LM	NA	Dementia
Solal-Celigny et al,[10] 1983	NA	CLL	NA	NA	LM	NA	NA
Steinberg et al,[11] 1985	M/38	CLL	III	Y	LM	NA	Lethargy, proptosis
Singh and Thompson,[12] 1986	M/56	CLL	II	Y	LM	NA	Ataxia, cranial nerve palsy
Boogerd and Vroom,[13] 1986	M/74	CLL	0	Y	LM	NA	Gait disturbance, tinnitus
Cash et al,[14] 1987	F/59	CLL	0	Y	LM	NA	Visual loss, legs weakness, sensory impairment
	M/57	CLL	0	Y	LM	NA	Headache, gait disturbance
Stagg and Gumbart,[15] 1987	F/66	CLL	III	Y	LM	NA	Headache, SIADH
Lustman et al,[16] 1988	NA	CLL	I	Y	SC	NA	Paraplegia, legs paresthesias
Currie et al,[18] 1988	M/76	CLL	III	Y	ON	NA	Visual loss
	F/45	CLL	III	Y	ON	NA	Visual loss
	M/67	CLL	IV	Y	ON	NA	Visual loss
Garofalo et al,[19] 1989	F/72	CLL	0	Y	H	At diagnosis	Headache, lethargy, confusion, leg/back pain
Michalevicz et al,[20] 1989	F/78	CLL	I	Y	SC	72 mo	Paraplegia
Grisold et al,[23] 1990	F/63	CLL	IV	Y	LM	3 mo	Gait disturbance, legs weakness, sensory neuropathy
Patton et al,[24] 1992	NA	CLL	NA	Y	B + LM	NA	NA
Fain et al,[25] 1992	F/57	CLL	NA	NA	P	NA	Visual loss
Ruiz et al,[26] 1992	M/79	CLL	IV	Y	LM	156 mo	Visual loss
Rubin and Harris,[27] 1993	M/73	CLL	0	NA	LM	NA	Confusion, visual loss, facial pain
Pohar et al,[29] 1993	M/63	CLL	NA	NA	B	NA	Gait disturbance, legs weakness
Paolini et al,[31] 1995	NA	CLL	II	Y	LM	NA	Headache
Cramer et al,[70] 1996	F/62	CLL	0	Y	LM	NA	Gait disturbance, legs weakness
Morrison et al,[32] 1998	M/61	CLL	IV	N	LM	4 wk	Ataxia, vertigo, occipital headaches
Hagberg et al,[33] 1997	NA	CLL	NA	Y	LM	NA	SIADH
	NA	CLL	NA	Y	LM	NA	SIADH
Miller et al,[34] 1997	M/44	CLL	0	Y	LM	NA	Visual loss, paresthesias
Garicochea et al,[35] 1997	NA	CLL	NA	NA	LM	NA	NA
Majumdar,[36] 1998	M/66	CLL	I	Y	SC	22 mo	Paraplegia, legs paresthesias
Perez et al,[37] 1998	M/65	CLL	0	Y	LM	At diagnosis	Headache, confusion, diplopia
Poplawska-Szczyglowska et al,[38] 1999	M/68	CLL/SLL	II	Y	B	At diagnosis	Hemiparesis, aphasia
Elliot et al,[39] 1999	M/52	CLL	0	Y	LM	At diagnosis	Left leg paresis, visual loss, back pain
Vogt-Schaden et al,[40] 1999	M/54	CLL	I-II	Y	LM	60 mo	Diplopia, facial and hypoglossal nerve palsy, left leg paresis
Marmont,[42] 2000	M/70	CLL	0	Y	LM	144 mo	Confusion, legs pain

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Table 2 (continued)

Study	Sex/Age	Disease	Rai Stage	Sys D	CNS Site	Time to CNS Disease	Clinical Manifestations
Wang et al,[43] 2000	M/81	CLL	IV	Y	LM	29 mo	NA
Rye et al,[44] 2001	M/61	CLL	IV	Y	P	At diagnosis	SIADH
Akintola-Ogunremi et al,[45] 2002	F/89	CLL	0	Y	LM	At diagnosis	Altered mental status
Estevez et al,[46] 2002	F/70	CLL/SLL	II	Y	Dura + B	NA	Ataxia, deafness, vision loss, hyperesthesia of the scalp
Brick et al,[47] 2002	M/77	CLL	0-I	Y	LM	48 mo	Headache, diplopia, cranial nerve palsy
Kaiser,[48] 2003	M/53	CLL	II	Y	B	At diagnosis	Focal jacksonian seizures
Remkova et al,[49] 2003	M/78	CLL	0	Y	LM	At diagnosis	Headache, lethargy, loss of vision
Nimubona et al,[50] 2004	F/43	CLL	0	Y	P	At diagnosis	Panhypopituitarism
Watanabe et al,[52] 2005	F/70	CLL	0-II	Y	LM	12 mo	Headache, ophthalmalgia, tinnitus, confusion
Knop et al,[53] 2005	M/83	CLL	II	Y	LM	32 mo	Diplopia
	F/68	CLL	I	Y	LM	94 mo	Facial nerve palsy, left leg paresis
	F/74	CLL	II	Y	LM	4 mo	Hyperesthesia, paresthesia
	M/42	CLL	II	Y	LM	54 mo	Asymptomatic
	F/53	CLL	III	Y	LM	55 mo	Paresthesia, neuropathic pain
Schmidt-Hieber et al,[54] 2005	M/71	CLL	I	Y	LM	6 mo	Paraparesis
Lange et al,[56] 2007	F/61	CLL	II	Y	LM	36 mo	Lower limbs weakness, left leg paresis
Kalac et al,[57] 2007	M/62	CLL	0-I	N	LM	At diagnosis	Right hemiparesis, lethargy, hallucinations
Giordano et al,[59] 2007	NA	CLL/SLL	NA	NA	B	NA	NA
Kiewe et al,[61] 2007	M/42	CLL	I	N	Dura	At diagnosis	Headache, diplopia, facial nerve palsy
Kakimoto et al, 2010	M/58	CLL	III	Y	B + LM	132 mo	Memory loss, progressive blinding
Kelly et al,[63] 2008	M/74	CLL/SLL	I	Y	Dura + B	At diagnosis	Left face and arm seizure and paresthesias
Hanse et al,[64] 2008	M/74	CLL	I	Y	LM	54 mo	Headache
	M/57	CLL	I	Y	LM	1 mo	Facial nerve palsy, L3 syndrome
	M/68	CLL	IV	Y	LM	75 mo	Confusion, headache
	M/71	CLL	III	Y	LM	53 mo	Diplopia, trigeminus nerve palsy, vertigo
	M/69	CLL	NA	Y	LM	108 mo	Diplopia, deafness
	M/65	CLL	I	Y	LM	36 mo	Left leg paresis, left face hypoesthesia
Calvo-Villas et al,[67] 2010	M/52 LM	CLL	I	Y	LM	60 mo	Headache, lethargy
	M/44	CLL	IV	Y	LM	24 mo	Headache, face dysesthesia, vision loss
	M/81	CLL	0	Y	LM	24 mo	Headache, lethargy, confusion
	F/64	CLL	IV	Y	LM	12 mo	Headache, diplopia

Abbreviations: B = brain; CLL = chronic lymphocytic leukemia; CNS = central nervous system; H = hypothalamus; LM = leptomeninges; NA = not available or not stated; ON = optic nerve; P = pituitary; SC = spinal cord; SIADH = syndrome of inappropriate antidiuretic hormone hypersecretion; SLL = small lymphocytic lymphoma; Sys D = systemic disease.

malignant cells. Under these circumstances, if a mass is readily accessible by biopsy, then histopathologic analysis of the specimen confirms its precise neoplastic nature. In this regard, 11 CLL cases (3 pituitary disease, 3 SLL, and the remaining dural involvement by CLL) were documented by brain biopsy.[6,25,29,44,46,48,50,58,61-63] The interpretation of CSF analysis in patients with CLL is not always straightforward. First, due to derangements of humoral and cellular immune functions, CNS opportunistic infections may be associated with false-positive cytologies. Viral meningitis is classically described as being associated with a lymphocytic CSF, but it must be remembered that polymorphonuclears (PMN) may predominate, especially early in the illness. Reactive nonclonal lymphocytosis is also seen in fungal infections and in 10% of bacterial meningitis, although a predominance of PMNs may be present in the early stages of these

Table 3 Diagnostic Procedures, Treatment, Response, and Outcome of the Patients With Documented Central Nervous System Involvement by Chronic Lymphocytic Leukemia and/or Small Lymphocytic Lymphoma

Study	Neuroimaging	CSF	Histology	Treatment	Response	Outcome
Amiel and Droz,[5] 1976	NA	NA	No	IT (MTX) + RT	CR	Alive
Nemoto et al,[6] 1978	NA	NA	Yes +	None	NR	Dead
Getaz and Miller,[7] 1979	NA	NA	No	IT (MTX)	NR	Dead
Liepman and Votaw,[8] 1981	NA	Positive	No	IT (MTX)	CR	Dead
	NA	Positive	No	IT (MRX) + RT	CR	Alive
Korsager et al,[9] 1982	NA	Positive	No	IT (MRX) + RT	CR	Alive
	NA	Positive	No	None	NR	Dead
Solal-Celigny et al,[10] 1983	NA	NA	No	IT (MTX)	CR	NA
Steinberg et al,[11] 1985	NA	Positive	No	IT (MTX) + RT	CR	Alive
Singh and Thompson,[12] 1986	NA	Positive	No	IT (MTX) + RT	CR	Alive
Boogerd and Vroom,[13] 1986	NA	Positive	No	None	NR	Dead
Cash et al,[14] 1987	NA	Positive	No	IT (MTX + araC) + RT	CR	Alive
	NA	Positive	No	IT (MTX + araC) + RT	CR	Alive
Stagg and Gumbart,[15] 1987	NA	Positive	No	IT (MTX)	CR	Alive
Lustman et al,[16] 1988	NA	NA	No	NA	NA	NA
Currie et al,[18] 1988	NA	NA	No	RT	PR	NA
	NA	NA	No	RT	PR	NA
	NA	NA	No	RT	PR	NA
Garofalo et al,[19] 1989	Positive	Positive	No	Ventricular shunt	NR	Dead
Michalevicz et al,[20] 1989	NA	Negative	No	DXM	NR	Dead
Grisold et al,[23] 1990	NA	NA	No	None	NR	Dead
Patton et al,[24] 1992	NA	NA	No	NA	NA	NA
Fain et al,[25] 1992	Positive	Positive	Yes +	Surgery	CR	Alive
Ruiz et al,[26] 1992	NA	Positive	No	NA	NA	NA
Rubin and Harris,[27] 1993	NA	NA	No	None	NR	Dead
Pohar et al,[29] 1993	Positive	NA	Yes +	RT	PR	Alive
Paolini et al,[31] 1995	NA	NA	No	I.V. (Flu)	CR	Alive
Cramer et al,[70] 1996	NA	Positive	No	IT (MTX + araC) + RT	CR	Alive
Morrison et al,[32] 1998	NA	Positive	No	IT (MTX) + RT	CR	Alive
Hagberg et al,[33] 1997	NA	NA	No	NA	NA	NA
	NA	NA	No	NA	NA	NA
Miller et al,[34] 1997	NA	Positive	No	IT (MTX + araC) + RT	CR	Alive
Garicochea et al,[35] 1997	NA	Only PCR	No	NA	NA	NA
Majumdar,[36] 1998	NA	Negative	Yes +	Surgery + RT + COP	CR	Dead after 42 mo
Perez et al,[37] 1998	Normal	Positive	No	IT (MTX) + RT	PR	Dead
Poplawska-Szczglowska et al,[38] 1999	Positive	Positive	No	IT (MTX)	PR	Dead after 6 mo
Elliot et al,[39] 1999	Positive	Positive	No	I.V. (Flu)	CR	Alive
Vogt-Schaden et al,[40] 1999	Normal	Only PCR	No	None	NR	Dead after weeks
Marmont,[42] 2000	Normal	Positive	No	IT (MTX) + RT	CR	Alive
Wang et al,[43] 2000	NA	Positive	No	IT Chemo + RT	CR	Dead
Rye et al,[44] 2001	Normal	NA	Yes +	I.V. (Flu)	PR	Dead

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Table 3 (continued)

Study	Neuroimaging	CSF	Histology	Treatment	Response	Outcome
Akintola-Ogunremi etal,[45] 2002	Normal	Positive	No	None	NR	Dead
Estevez et al,[46] 2002	NA	NA	Yes +	NA	NA	NA
Brick et al,[47] 2002	NA	Positive	No	IT (MTX + araC)	CR	Alive
Kaiser,[48] 2003	NA	Negative	Yes +	RT	CR	Alive after 1 y
Remkova et al,[49] 2003	Normal	Positive	No	IT (MTX + DXM)	CR	Alive
Nimubona et al,[50] 2004	Positive	Negative	Yes +	Surgery	CR	Alive
Watanabe et al,[52] 2005	Normal	Positive	No	IT (MTX + DXM) + R	CR	Alive
Knop et al,[53] 2005	Normal	Positive	No	None	NR	Dead after 1 mo
	Normal	Positive	No	RT	PR	Dead after 5 mo
	Normal	Positive	No	IT (MTX)	CR	Dead after 6 mo
	Normal	Positive	No	I.V. (Flu)	CR	Alive after 20 mo
	Positive	Positive	No	IT (MTX + araC + DXM)	PR	Dead after 3 mo
Schmidt-Hieber et al,[54] 2005	Normal	Positive	No	IT (MTX + araC + DXM)	NR	Dead
Lange et al,[56] 2007	Positive	Positive	No	IT (MTX + liposomal araC) + COP	PR	Dead after 6 mo
Kalac et al,[57] 2007	Normal	Positive	No	IT (DXM) + CLB	CR	Alive
Giordano et al,[59] 2007	NA	NA	No	NA	NA	NA
Kiewe et al,[61] 2007	Positive	Negative	Yes +	Surgery + DXM + RT	CR	Alive
Kakimoto et al, 2010	Positive	Negative	Yes +	I.V. (MTX + Flu) + RT	NR	Dead after 6 mo
Kelly et al,[63] 2008	Positive	NA	Yes +	RT	NA	NA
Hanse et al,[64] 2008	Normal	Positive	No	IT (MTX + araC) + CLB	CR	Alive
	Positive	Positive	No	IT (MTX + araC) + RT + CLB	CR	Alive
	Normal	Positive	No	IT (MTX) + CHOP	CR	Alive
	Normal	Positive	No	IT (MTX + araC) +RT	PR	Dead after 5 mo
	NA	Positive	No	IT (MTX + araC + DXM) + I.V. (MTX + araC)	CR	Alive
	Positive	Negative	No	IT (Mtx + araC + DXM) + I.V. (MTX + araC)	CR	Alive
Calvo-Villas et al,[67] 2010	NA	Positive	No	IT (liposomal araC) + RT	CR	Alive
	NA	Positive	No	IT (liposomal araC)	CR	Dead after 12 mo
	NA	Positive	No	IT (liposomal araC)	CR	Dead after 3 mo
	NA	Positive	No	IT (liposomal araC)	CR	Alive

Abbreviations: araC = cytarabine; CHOP = cyclophosphamide/doxorubicin/vincristine (Oncovin)/prednisolone; COP = cyclophosphamide/vincristine (Oncovin)/prednisolone; CLB = chlorambucil; CR = complete response; DXM = dexamethasone; Flu = fludarabine; IT = intrathecal; I.V. = intravenous; MTX = methotrexate; NA = not available or not stated; NR = no response; PCR = polymerase chain reaction; PR = partial response; R = rituximab; RT = radiotherapy.

infections. The cornerstone for the diagnosis of CLL leukemic infiltration of the CNS is accomplished by proving the monoclonality of the cytologically abnormal malignant lymphocytes in the CSF. Even so, the demonstration of monoclonal B cells in CSF does not allow affirmation with certainty of the presence of tumoral CNS involvement in such infectious cases because patients with CLL who have high circulating malignant B cells may show infiltration of clonal lymphocytes in sites of CNS inflammation as a part of a reactive process.[72] Second, traumatic introduction of monoclonal B cells into the CSF during lumbar puncture occurs 20% of the time and would result in an artificial increase in white blood cells from 1 for every 500 to 1000 red blood cells in the CSF and hence be responsible for the contamination of the CSF with malignant B cells. To avoid misinterpretation with neoplastic infiltration, subsequent lumbar punctures can be performed to ascertain if the presence of malignant cells is fleeting or is related to a true neoplastic CNS infiltration. Third, results of 1 study suggested that, in patients with lymphoid neoplasms such as CLL, the presence of a neoplastic B-cell clone population in the CSF is not diagnostic of clinically significant involvement of the CNS but may be caused by the trafficking of lymphocytes, although a longer follow-up of the patients is needed to confirm this observation.[72]

An appropriate and optimal systemic treatment for CNS involvement of CLL still remains to be established. However, management of CNS symptoms with single or triple intrathecal chemotherapy given twice a week for 4 weeks and then once weekly for a total maximum of 12 administrations, followed or not by radiotherapy, is usually the rule. The body's blood-brain barrier does not allow many

chemotherapy drugs given systemically to get to the CSF. Water-soluble ionized molecules given intravenously as single injections do not penetrate the blood brain-barrier to any great degree. The principal drugs used to treat CNS disease in CLL are methotrexate (MTX), cytarabine, steroids, and fludarabine. MTX is an antimetabolite drug that inhibits dihydrofolate reductase. It is poorly transported across the blood-brain barrier, and therapeutic concentration in CNS only occurs with high-dose therapy or by an intrathecal administration in which it presents a highly uniform distribution in the intrathecal space, which produces the most consistent levels of CSF compared with other routes of administration.[73] Cytarabine, a pyrimidine nucleoside that inhibits the DNA polymerase, has a poor and unpredictable absorption after oral administration. Cytarabine is administered intravenously or intrathecally. Anyhow, data regarding its capacity to cross the blood-brain barrier are limited, and, when given intrathecally, most of the dose diffuses into the systemic circulation.[74] Its liposomal formulation offers a better form to deliver this drug into the CNS in a sustained form. The steroid dexamethasone has poor brain penetration.[75] Nonetheless, given intrathecally, all of the prodrug is converted into its active form and attains steady levels in the CSF.[76] Fludarabine, a purine nucleoside, has been shown to diffuse into the CNS by a specific transport mechanism in animal models.[77] Because the arachnoid space and nerve roots are not protected by the blood-brain barrier, a good control of leptomeningeal and cranial nerves disease could be achieved in patients with CLL and of leptomeningeal disease with this drug, as has been suggested by a study.[53]

From the available data in the medical literature, dura or parenchymal infiltration and leptomeningeal invasion occurred in 12 and 55 patients, respectively. Dura and parenchymal disease therapy was based on radiotherapy (n = 3), surgery (n = 3), radiotherapy plus surgery (n = 1), chemotherapy (n = 2), or none or no data available (n = 3), and the responses were varied. Patients with leptomeningeal disease (n = 55) were treated with radiotherapy alone (n = 1), intrathecal MTX plus systemic chemotherapy (n = 7), intrathecal MTX plus radiotherapy (n = 6), intrathecal MTX, and cytarabine or steroids with or without radiotherapy, and systemic chemotherapy (n = 16), intrathecal liposomal cytarabine with or without radiotherapy and systemic chemotherapy (n = 5), intravenous fludarabine as monotherapy or combined with MTX plus radiotherapy (n = 4), systemic chemotherapy with or without radiotherapy (n = 3), and no therapy or unknown (n = 13).

A higher number of clinical neurologic and laboratory complete responses as well as better outcomes were observed among patients treated with an intrathecal combination of chemotherapy with or without radiotherapy (n = 22), with a complete response in 19 of 22 patients, 2 of 22 with partial responses, and 1 of 22 without response, whereas fewer good response rates and outcomes were associated with radiotherapy or intrathecal MTX used alone.

Systemic fludarabine has been used in 4 instances to treat the leptomeningeal invasion, and, in 3 of 4 patients, complete neurologic disease remission was observed.[39,44,58,63] Intrathecal liposomal cytarabine given as monotherapy appears to be a good approach because it showed promising results. In a retrospective study that involved 7 patients, of whom 4 had leptomeningeal invaded by CLL, all attained complete clinical and laboratory responses.[67] Although fludarabine and liposomal cytarabine can be favorable therapeutic options for CNS invasion, further larger series studies are necessary to validate their efficacy. Prognosis could be improved by a timely diagnosis and prompt and aggressive therapy, which allows induction of durable complete clinical and laboratory resolution of neurologic abnormalities. Nevertheless, prognostic factors for the risk of CNS involvement remain to be determined yet and are urgently required to allow a better management of these situations.

CLL and Hypophysis and/or Hypothalamus Disease

In very rare instances, CLL invasion of the sella turcica is observed, and a diagnosis is made as a consequence of symptomatic disease. The first reported case occurred in a young patient with relapsed CLL manifested as visual disturbances due to an isolate sellar mass without systemic disease, which simulated a pituitary (hypophysis) tumor. The final diagnosis was only obtained after an autopsy.[6] In another patient, direct involvement of the pituitary gland resulted in adrenal insufficiency and gonadotrophin deficiency. Moreover, the extension of the lesion upward into the suprasellar region culminated in compression of the optic chiasm and bitemporal hemianopsia ensued.[25] When no traumatic injury is present, this clinical finding is pathognomonic for a pituitary tumor. In an extreme case, a pituitary tumor consists of CLL cells presented as panhypopituitarism (hyperthyroidism, hyperprolactinemia, hypocortisolemia). A complete response was attained after surgery, and the patient was receiving hormonal supplementation.[50] Hyponatremia, of 115 mmol/L, due to an inappropriate antidiuretic hormone secretion syndrome is another rare complication of CLL and may arise as a secondary complication of CNS infections, leptomeningeal invasion, and, very uncommonly, direct pituitary involvement. In this specific case, neuroimaging was perfectly nonspecific and definitive diagnosis was made at postmortem.[44]

Despite the apparent rarity of pituitary invasion, autopsy studies revealed that, in fact, the pituitary is one of the most often involved sites in the CNS by CLL.[71] Hypothalamic invasion by CLL is also possible and was diagnosed in only 1 instance in a patient with a clinical picture of intracranial hypertension, with headache and confusion due to obstruction of the foramina of Monro and who required urgent surgical decompression without success.[19]

CLL and RS of the Brain

RS is defined as the transformation of a low-grade CLL and/or small lymphocytic lymphoma (SLL) to a more aggressive high-grade malignant form, usually diffuse, large B-cell, non-Hodgkin lymphoma and, more unusually, Hodgkin lymphoma. RS is not truly a second malignancy because the CLL clone appears to be involved. However, much debate exists about whether the transformation represents a common origin, with the emergence of a more malignant clone of CLL cells or if a distinct independent clonal evolution is the case.[78] The incidence of RS varies between 3% and 10.6% of patients with CLL, and its involvement of the CNS is extremely rare, with only 17 cases described so far (16 non-Hodgkin lymphoma and 1 Hodgkin lymphoma) since the first report in 1988. (Tables 4, 5).[17,21,22,28,30,41,51,55,58,60,65-67,79] In order of frequency, the brain parenchyma is the preferred affected site and has a dismal prognosis even after treatment, followed by the leptomeninges and the dura mater. Isolated extranodal (brain) involvement without sys-

Table 4 Clinical Characteristics, Type of Neurologic Involvement and Symptoms of the Patients With Documented CNS Involvement by Richter Syndrome

Study	Sex/Age	Disease	Rai Stage	Sys D	CNS Site	Time to CNS Involvement, mo	Clinical Manifestations
Lane et al,[17] 1988	M/45	CLL/RS	NA	Yes	B	NA	NA
O'Neill et al,[21] 1989	NA	CLL/RS	NA	No	B	NA	NA
	NA	CLL/RS	NA	No	B	NA	NA
Bayliss et al,[22] 1990	NA	CLL/RS	NA	NA	B	NA	NA
Robertson et al,[28] 1993	NA	CLL/RS	NA	NA	B	NA	NA
Mahé et al,[30] 1994	NA	CLL/RS	NA	No	B	NA	NA
	NA	CLL/RS	NA	No	B	NA	NA
Agard et al,[41] 1999	NA	CLL/RS	NA	Yes	B + LM	NA	Cranial nerve palsies
Robak et al,[51] 2004	F/60	CLL/RS	NA	Yes	B	NA	Stroke
Resende et al,[55] 2005	M/74	CLL/RS	I	Yes	B	72	Gait disturbance, confusion
Ghofrani et al,[58] 2007	M/64	CLL/RS	II	Yes	Dural + B	60	Headache, vision loss
Bagic et al,[60] 2007	F/58	CLL/RS	NA	No	B	36	Left leg paresis
Denier et al,[65] 2009	M/80	CLL/RS	II	Yes	LM	24	Confusion, diplopia, right leg paresis; VI nerve palsy
Almhanna et al,[66] 2009	M/65	CLL/RS		Yes	B	96	NA
	F/68	CLL/RS	IV	Yes	LM	36	Trigeminus nerve palsy
	M/79	CLL/RS	IV	Yes	LM	60	Gait disturbance, facial nerve palsy, lower limbs weakness
	F/78	CLL/RS	IV	Yes	LM	24	Headache

Abbreviations: B = brain; CLL = chronic lymphocytic leukemia; CNS = central nervous system; LM = leptomeninges; NA = not available or not stated; RS = Richter syndrome; Sys D = systemic disease.

Table 5 Diagnostic Procedures, Treatment, Response, and Outcome of the Patients With Documented Central Nervous System Involvement by Richter Syndrome

Study	Neuroimaging	CSF	Histology	Treatment	Response	Outcome
Lane et al,[17] 1988	NA	Positive	No	NA	NA	NA
O'Neill et al,[21] 1989	NA	NA	No	NA	NA	NA
	NA	NA	No	NA	NA	NA
Bayliss et al,[22] 1990	NA	NA	No	NA	NA	NA
Robertson et al,[28] 1993	NA	NA	No	NA	NA	NA
Mahé et al,[30] 1994	NA	NA	No	NA	NA	NA
	NA	NA	No	NA	NA	NA
Agard et al,[41] 1999	Normal	Positive	No	NA	NA	Alive
Robak et al,[51] 2004	Positive	Negative	Yes +	RT	CR	
Resende et al,[55] 2005	Positive	Negative	Yes +	IT (MTX + araC + DXM) + RT + CLB	CR	Dead after 5 mo
Ghofrani et al,[58] 2007	Positive	NA	Yes +	R-CHOP + RT	PR	Dead after 3 mo
Bagic et al,[60] 2007	Normal	NA	Yes +	RT + R	NA	NA
Denier et al,[65] 2009	Normal	Negative	No	IT (MTX + araC + DXM)	NR	Dead
Almhanna et al,[66] 2009	NA	Positive	No	NA	NA	NA
	NA	Positive	No	IT (liposomal araC)	CR	Dead after 1 mo
	NA	Positive	No	IT (MTX + araC + DXM + liposomal araC)	CR	Dead after 1 mo
	NA	Positive	No	IT (MTX + araC + DXM + liposomal araC)	CR	Alive

Abbreviations: araC = cytarabine; CHOP = cyclophosphamide/doxorubicin/vincristine (Oncovin)/prednisolone; CLB = chlorambucil; CR = complete response; CSF = cerebrospinal fluid; DXM-dexamethasone; I.V. = intravenous; IT = intrathecal; MTX = methotrexate; NA = not available or not stated; NR = no response; PR = partial response; R-CHOP = rituximab/cyclophosphamide/doxorubicin/vincristine (Oncovin)/prednisolone; RT = radiotherapy.

temic disease occurs in up to 45% of cases.[55] Neurologic manifestations appear abruptly and range from confusional states, gait disorders, monoparesis, and cranial nerve palsies to signs of intracranial hypertension (headache, papilledema). In 1 report, stroke was the inaugural manifestation of a cerebral RS.[51] Neuroimaging reveals a hypodense area of the brain with or without contrast enhancement or can be nonspecific if the meninges are the predominantly affected site.[30,41] In the latter scenario, immunophenotyping of CSF is helpful to the final diagnosis. It should be emphasized that CNS (brain parenchyma) RS shares similar neuroimaging characteristics with multiform glioblastoma.[55] However, brain biopsy followed by immunohistochemical studies yield the definitive diagnosis. Treatment consists of radiotherapy and intrathecal chemotherapy (plus immunochemotherapy if systemic disease is present). In 2 patients, surgery was performed: 1 for a Hodgkin variant of cerebral RS and another for a relapsed brain RS in which a frontal lobectomy was done without incident. Both patients eventually died.[55,58] Survival has been dismal because the patient's disease usually is advanced at the time of presentation and have a poor response. Notwithstanding, therapy can improve the symptoms and the quality of life. Recently, in a retrospective study, 3 patients with RS of the CNS treated with intrathecal liposomal cytarabine achieved a sustained complete response, which included resolution of the neurologic symptoms and clearance of the CSF malignant cells, without relevant drug adverse effects.[67] Although the preliminary results are promising, prospective randomized studies are needed to confirm this.

CLL and Ophthalmology Disease (Retinopathy and Optic Neuropathy)

Ophthalmic disease in CLL is very uncommon. In 1 prospective study, it was found that CLL-associated ocular complications included bilateral posterior subcapsular cataract after radiotherapy, unilateral conjunctival vascular anomalies, and unilateral acute retinal necrosis. Those manifestations were not related to the CLL stage.[80] As an extension of the CNS, the retina can be affected by CLL in different ways. Retinal detachments accompanied by ocular pain or decreased vision may be the first sign of the underlying CLL or even RS and are a consequence of infection or, more rarely, direct tumor infiltration or hyperviscosity.[81-85] Peripheral retinal microaneurysm due to prolonged leukocytosis can induce peripheral capillary dropout, vascular stagnation, microaneurysm formation, and peripheral proliferative retinopathy.[86] Cancer-associated retinopathy, although not considered a paraneoplastic neurologic syndrome anymore, was described in 1 instance in a patient with CLL in whom the presence of serum antibodies to retinal enolase were detected.[87] Infectious necrotizing retinopathy with ensuing optic atrophy or total retinal detachment and proliferative vitreoretinopathy is another possible complication of CLL-associated retinal disease. CLL and a CLL-therapy–induced state of immunosuppression render the patients prone to opportunistic infections. The simultaneous occurrence of infection with multiple agents can happen. Triple viral retinitis (herpes simplex, varicella zoster, and cytomegalovirus) and retinitis due to toxoplasmosis with concomitant ocular reactivation of varicella-zoster virus and cytomegalovirus were reported under those circumstances. Specific antimicrobial treatment may resolve retinal necrosis, but visual recovery remains poor due to optic nerve atrophy.[88-91] However, results of a report suggest that adding intravenous gamma globulin may promote humoral immunity and can be beneficial for a rapid visual improvement.[92] Iatrogenic retinopathy was described once in a patient treated with the experimental drug denileukin diftitox (a fusion protein of portions of diphtheria toxin and interleukin (IL)-2 that targets IL-2 receptors on malignant cells and induces apoptosis.[93] Optic nerve neuropathy is another condition that threatens the vision, because progressive optic atrophy is generally followed by loss of acuity and the visual field. Two types of involvement can occur: prelaminar (the tumor mass can be seen along the papilla) and retrolaminar (signs of papillary edema are evident). Optic nerve infiltration occurs in approximately a fourth of patients with CLL and with leukemic meningitis, and can be an early manifestation of CLL or can occur later throughout the disease.[18,94-96] Chemotherapy plus radiotherapy is the mainstay of treatment, with a good outcome. When facing a patient with a previous diagnosis of CLL and who presents with a sudden loss of vision, a full ophthalmologic examination is mandatory followed by neuroimaging. If a papillar mass or papilledema is present, then the diagnosis of optic nerve infiltration by CLL should be considered. Because a lesion biopsy is not always feasible and knowing that concurrent meningeal infiltration and optic neuropathy may occur, immunophenotyping of CSF lymphocytes is useful in differentiating leukemic optic nerve infiltration from other causes of optic nerve damage.

CLL and Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) refers to a neurologic disorder characterized by myelin destruction of the CNS caused by JC virus (JCV), named after the initials of the patient in whom it was first discovered. The virus is ubiquitous, found in at least 85% of the general adult population. It remains inactive in healthy individuals and causes disease only when the immune system has been severely compromised, such as in people with human immunodeficiency virus or AIDS, or hematologic malignancies, and, in organ transplant recipients who take immunosuppressive drugs to avoid rejection of the transplanted organ. PML is a progressive disease because it continues to get worse and often leads to serious brain damage that is multifocal. However, it is possible for an individual with PML to have only 1 brain lesion instead of several lesions, which sometimes may cause a problem in the differential diagnosis. The term leukoencephalopathy means that the disease mainly affects the white matter of the brain (more precisely, the axonal myelin of the oligodendrocytes, and it produces cellular intranuclear inclusions), although there are some rare cases in which the gray matter neurons are also involved. Symptoms include weakness or paralysis, vision loss, impaired speech, and cognitive deterioration. Focal neurologic signs include aphasia, hemiparesis, ataxia, cortical blindness, and, less frequently, head tremor. Focal signs tend to be related to posterior brain (occipital lobes) lesions. Conjugate gaze abnormalities are common, and this is the initial presentation in >30% of patients. Abnormalities may progress to quadriparesis and coma. Occasionally, neurologic signs are more diffuse rather than focal. PML is diagnosed by testing for JCV DNA in CSF or in a brain biopsy specimen. PCR of the CSF has been shown to be highly specific (92%-99%) and sensitive (74%-93%) for the detection of JCV in patients with PML.

Stereotactic brain biopsy is the criterion standard to diagnose PML. Histology results reveal single or multiple areas of demyelination that contain JCV-infected oligodendrocytes with enlarged nuclei in the periphery of the lesions, reactive gliosis with bizarre astrocytes, lipid-laden macrophages phagocyting myelin, and cellular debris. Although the demonstration of JCV in the brain is helpful, it is not necessary to make the diagnosis. Patients in whom CSF and brain PCR for JCV are negative can be diagnosed by immunolabeling of glial cells by anti-JCV antibody.[97] Characteristic evidence of the damage caused by PML in the brain can also be detected on magnetic resonance images, which classically show multifocal nonenhancing lesions without mass effect. Lesions are predominantly located in the periventricular and subcortical frontal and parieto-occipital white matter, followed by a decreasing likelihood in the brainstem, cerebellum, thalamus, corpus callosum, and, rarely, the cervical and thoracic spinal cord. These lesions are typically asymmetric, diffuse, subcortical, and localized to the white matter. Treatment trials with cidofovir, topotecan, and interferon alfa have been inconclusive.[98] Other antiviral agents that have been studied as possible treatments for PML include IL-2, but this research is still preliminary. Cytarabine, a chemotherapy drug used to treat certain cancers, has been prescribed on an experimental basis for a small number of patients with non-AIDS PML.[99] It is reported to have stabilized the neurologic condition of a minority of these patients. There also is evidence to suggest that the JCV uses serotonin 5HT2A receptors to infect glial cells. Isolated case reports have demonstrated that serotonergic receptor antagonists, such as risperidone and mirtazapine, might be useful in the treatment of PML.[100,101] More studies are needed to confirm this benefit. Cellular immunity is the mainstay of defense against JCV. CD4+ helper T lymphocytes recognize virus particles and stimulate CD8+ cytotoxic T lymphocytes (CTL). The presence of JCV-specific CTL is associated with prolonged survival in patients with PML. Immune humoral and cellular dysfunctions are inherent to CLL, and patients more frequently die of infections than the malignancy itself. Additional immunosuppression caused by CLL therapy also contributes and acts as a trigger to the worsening of cell-mediated immunity in CLL. In this context, since the first description of CLL-associated PML in 1958,[102] establishment of more intense chemotherapy regimens, including the purine analogue fludarabine or even the monoclonal antibody rituximab, contributed to the increasing amount of PML cases observed in recent years.[103,104] A decrease in the CD4+ and CD8+ lymphocyte subpopulations counts to levels below 200 cells/μL is observed after the initial 3 courses of treatment with fludarabine, and the recovery is slow.[105] Cladribine, another purine analogue used in some instances to treat CLL, also is associated with a great suppression of CD4+ counts. These low counts may persist for a median period of time of 40 months after treatment.[106] PML in the context of treatment-naive patients with CLL has lost ground, and, since 1990, 90% of the cases of PML observed among patients with CLL occurred in those treated with purine analogues.[107-119] In an univariate analysis, 3 significant risk factors for developing PML were identified: age >55 years, male sex, and CD4 cell count ≤200 cells/μL.[117] The exact incidence of CLL-related PML is difficult to ascertain because the diagnosis is based on clinical findings and is not usually done until a postmortem examination is performed. Besides, variable disparities in case reporting and incomplete reporting and data on the patients with purine-associated PML cases, allied to the nature of the studies done so far, which mainly include case studies and pooled case series reviews contribute to this issue.[118] To illustrate this, the PML incidence varied in 1 series that comprised 962 patients with CLL from 0.52%[119] to a high value of 5% in 60 patients with CLL treated with fludarabine.[4] In another recently published series, the incidence in 45 patients with CLL and treated with fludarabine or monoclonal antibodies was 6.6%.[118] Moreover, in another retrospective study, which included patients with CLL diagnosed between January 2000 and June 2008, it was noted that the incidence rate of PML in the CLL cohorts, was 11.1 (range, 0.28-61.74) per 100,000 person-years.[120] The median interval from purine analogues to PML was 11 months according to 1 study.[117] The median time of survival in patients with CLL and with PML is 3 months (range, 1-28 months) according to 1 study and 4.3 months in another analysis.[117,121] Until efficacious treatment is discovered for the treatment of PML induced by a JCV opportunistic infection, the prognosis continues to remain very poor. As a final reminder, clinicians who deal with patients with CLL should be aware of the potential for PML development, principally in those patients previously or currently being treated with agents that impair T-cell function, such as those used nowadays as up-front therapy for CLL.

CLL and Second Malignant Neoplasms (Brain Tumors)

Many studies and surveys have established that patients with CLL are more prone to develop second neoplasms when compared with the general population. However, the first study to report an association between CLL and the risk for developing brain cancer was a retrospective study that involved 81 patients with CLL, of whom 16 were found to have another malignant neoplasm subsequent to CLL diagnosis, which translated into a 1.7-fold increased risk for the appearance of second neoplasms. Among them, brain cancer occurred unexpectedly at a higher incidence. Four patients with CLL had multiple cancers, and, curiously, 1 patient had a triple cancer (astrocytoma, breast cancer, and melanoma).[122] In another, larger study, that comprised 9456 patients with CLL, 840 developed second neoplasms with an observed-to-expected ratio [O-E] = 1.28. Brain tumors were more prevalent, principally in men (O-E = 1.98). After CLL diagnosis, the risk of second neoplasms was not affected by the initial treatment category and remained constant along the timeline according to that study.[123] It should be noted that, in up to a third of patients with CLL who develop a second malignancy, a spontaneous remission of CLL precedes the diagnosis of the second malignancy by months or years. More recently, in a study that quantified the risk of second cancers among 16,367 patients with CLL in the population-based SEER (Surveillance, Epidemiology and End Results) Program, the overall O-E ratio was 1.20, with both groups of patients who received treatment (first course) and no treatment at all having the same risk. In that report, 22 of 16367 patients with CLL had brain cancer (16 glioblastomas, 3 meningiomas, 2 astrocytoma, and 1 glioma), and it was reconfirmed that the male sex is at higher risk for developing brain cancer (O/E =1.91).[124] Although second neoplasms occur with increased frequency in patients with naive or treated CLL, it is interesting to note that, paradoxically, their frequency and aggressiveness can be higher after treatment with nucle-

oside analogue therapy.[125] Impaired humoral and cellular immunity in CLL allied to therapy-related immunosuppression may explain, in part, the added risk of secondary neoplasms and, even more rarely, the occurrence of multiple tumors. However, to date, there is not any evidence or strong association that links immunosuppression to the risk of developing glioblastomas. So, there must be other mechanisms yet to be discovered to justify the increased risk for brain cancer in patients with CLL. In this regard, viral infections are an area to be explored. Because CLL is an indolent disease in most of the cases, the clinician must stay alert for the possibility of occurrence of other cancers, namely brain cancers after a CLL diagnosis, and they should be treated as they would be in patients without CLL.

CLL and CNS Bleeding

Hemorrhagic complications in CLL are most often related to thrombocytopenia either due to decreased megakaryopoiesis caused by diffuse CLL bone marrow infiltration or to increased peripheral platelet consumption by platelet autoantibodies (immune thrombocytopenia). Therapy-related immune thrombocytopenia also constitutes a rare adverse effect of some agents used to treat CLL, such as alemtuzumab, and in this context, a fatal CNS hemorrhage was described, despite discontinuation of this drug.[126] CNS bleeding as a neurologic complication associated with CLL is generally an extremely unusual event. Solely 2 isolated cases of a subdural hematoma were reported to date: 1 in a patient with CLL, which caused focal neurologic signs and with a good outcome after local treatment; and 1 diagnosed at autopsy.[127,128] In 2 larger retrospective studies, 1 that involved 75 patients with CLL, brain hemorrhage constituted 1 of the major causes of death, with an incidence of 7%,[129] whereas, in another, 1 cohort that comprised 962 patients with CLL, only 1 patient (0.1%) presented intracranial hemorrhage.[4] Despite the discrepancies of these numbers, CNS bleeding during the course of CLL is a very rare event but still an important occurrence of which to be aware.

CLL and CNS Infections

A major issue that patients with CLL have to deal with is the increased frequency and severity of infectious complications, which are related to the underlying alterations in immune function, both humoral immunity (hypogammaglobulinemia) and cellular qualitative and quantitative defects in B cells, T cells, NK cells, neutrophils, and the monocyte and/or macrophage lineage that are inherent to the disease process, to its progression, and further complicated by the immunosuppressive properties of the drugs used to treat CLL. Opportunistic infections are a serious cause of morbidity and mortality in patients with CLL. It is estimated that up to 80% of patients with CLL will develop infectious complications at some time in their disease course, with infections accounting for up to 60% of deaths. It is important to underscore that patients with CLL undergoing chemotherapy are not only at risk of acquiring infections but also at risk of reactivation of latent infections. In treatment-naive patients or those treated with chlorambucil, pulmonary infections are frequently caused by bacteria such as *Streptococcus pneumonia, Staphylococcus aureus,* and *Haemophilus influenzae*. With the advent of more potent drugs, such as the purine analogues (eg, fludarabine) and the monoclonal antibodies rituximab and alemtuzumab, the spectrum of organisms that cause infections in these patients is changing from common bacterial organisms to fewer common opportunistic pathogens, such as *Pneumocystis jiroveci, Listeria monocytogenes*, herpes viruses (herpes simplex virus [HSV], [CMV], EBV) and fungus (*Candida, Cryptococcus, Aspergillus*).[130] With regard to the sites of infection in patients with CLL, the CNS is no exception. PML due to opportunistic infection by JCV was already mentioned in a previous section. Here, discussion will focus on CNS infections caused by other agents. The most common CNS infection in patients with CLL is herpes zoster meningoencephalitis. In a retrospective study, 69 of 109 patients with CLL had herpes zoster infection,[4] which constituted the main complication among the spectrum of all possible neurologic complications associated with CLL. Besides meningoencephalitis, patients present with trigeminal zoster or disseminated zoster; the symptoms include headache, altered mental state, and lethargy. Antiviral treatment with acyclovir is associated with good responses.[131] Subacute HSV type 1 encephalitis as an initial presentation of CLL was reported only in 1 instance. The rarity of this type of infection in CLL is remarkable because HSV type 1 encephalitis is the most common cause of adult encephalitis worldwide.[132] Toxoplasmosis caused by *Toxoplasma gondii* is another opportunistic infection that occurs de novo or as a reactivation of a previous latent infection in an immunocompromised host, such as in the CLL setting.[90,133] Cerebral toxoplasmosis presents as multiple necrotizing lesions, frequently in the deep central nuclei, posterior fossa, or lobar regions at the gray-white junction. Microglial nodule inflammation accompanied by extensive necrosis is commonly seen. Neuroimaging studies usually show ring-enhanced lesions. The diffuse, non-necrotic, "encephalitic" form of cerebral toxoplasmosis, which was thought to be unique in AIDS-associated immunodeficiency, also was described for the first time in a patient with advanced disease stage CLL.[134] Coexistence of brain toxoplasmosis with other neurologic infectious agents (JCV; herpes zoster and CMV) also is possible and illustrates well the degree of immunosuppression.[88,135] CMV infection in CLL mainly affects the retina and was already discussed. Among the CNS opportunistic fungal infections in patients with CLL, meningoencephalitis by *Cryptococcus neoformans* is one of the most serious. Although being a treatable condition with antifungals, patients who are fluconazole resistant have been reported, which is unusual among patients without AIDS.[136] It often is difficult to reach a definitive diagnosis of cryptococcal meningitis in patients who are negative for human immunodeficiency virus, especially in patients with an immunosuppressed condition, T-cell suppression may present with less typical clinical manifestations of meningitis, and a delayed diagnosis is an important issue, with a reported crude mortality of 19.1%.[137] Adverse prognostic factors that predict treatment failure are steroid treatment, leukocytosis, mental status, high opening pressure during lumbar puncture, low CSF glucose level, <20 leukocytes/mL^3 in CSF, positive CSF smear, evidence of disseminated disease by positive blood cultures or elevated antigen titers in the blood or CSF, mental changes, age >60 years, and underlying malignancies.[138] Other more uncommon agents to take into account in a patient with CLL and with suspected CNS infection are *Listeria,* which can cause a fulminant meningoencephalitis[139]; pneumococcal meningitis; cerebral *Aspergillosis,* which presented in 1 instance as an aspergillus brain emboli[4] and also was

described in a relapsed patient with CLL who was being treated with a combination of alemtuzumab and steroids, and who achieved a complete recovery after prompt fungal therapy[140]; and infection by *Borrelia burgdorferi,* which was diagnosed in a patient with untreated CLL and with a suspected viral encephalitis but whose serologic analysis of CSF sample precluded the initial hypothesis, and confirmation of Borreliae was done by enzyme-linked immunosorbent assay.[57]

CLL and Therapy-Related Neurologic Disease

Therapeutic advances in CLL, in addition to the benefits in terms of response rates and better disease control, also has resulted in the appearance of some adverse effects, for example, neurotoxicity. This has an important impact on quality of life and may even limit the use of the treatment. With the increasing use of multiple modality therapy, neurotoxicity can be induced by synergistic or additive effects of antineoplastic therapy, so early diagnosis is essential because a delayed recognition generally has irreversible consequences. Regarding the agents commonly used to treat CLL, all of them present a more or less marked profile of neurotoxicity. Chlorambucil, an alkylating agent used to treat CLL in the prepurine analogue era is still an option in older patients who have contraindications to the more recent drugs. This drug has been associated with cases of myoclonus and seizures, even in therapeutic dosages.[141,142] The purine analogue fludarabine, beyond being associated with an increased risk of JCV-induced PML, causes mild and reversible neurotoxicity in about 15% of patients with CLL in the conventional dosage.[143] Advanced age (>60 years) and higher than the recommended doses are risk factors for purine analogue–associated neurotoxicity. Fludarabine presents a dose-relationship neurotoxicity profile. At higher doses (>50 mg/m^2/d for 5 days), it causes severe irreversible CNS toxicity and death.[143,144] Neural alterations, such as diffuse white matter loss on CNS imaging, are typical, and clinical neurologic complications include blindness and encephalopathy.[145] In the context of hematopoietic stem cell transplantation, fludarabine-induced toxic leukoencephalopathy affects up to 2.4% of patients and can be subdivided in 3 entities: posterior reversible encephalopathy syndrome, characterized by reversible seizures, headache, vision disturbances, and mental derangements; acute toxic leukoencephalopathy; and other leukoencephalopathies, which are generally fatal due to permanent cognitive dysfunction.[146] The monoclonal antibody rituximab associated neurotoxicity is very rare and includes occasional cases of PML, posterior reversible encephalopathy syndrome, and hyperammonemic encephalopathy.[147,148] Development of moderate or worse neurotoxicity should result in discontinuation of that drug. Other agents used as part of the treatment regimen for CLL, such as cyclophosphamide, bendamustine, or oxaliplatin, also were described in anecdotal reports as having potential neurotoxicity. However, no single case was described in the context of CLL management. Notwithstanding the absence of reported neurotoxicity with the use of these agents in CLL, the possibility of severe neurologic sequelae related to their use should raise the clinician awareness of the possibility of such drug adverse effects.

Besides neurotoxicity, CNS infection is another collateral effect associated with CLL therapy. PML incidence is higher among patients with CLL treated with the purine analogue fludarabine. High and prolonged corticosteroid use or steroid combination–based therapies aggravate the immune function and host defense mechanisms, predisposing patients to a variety of infections that include bacterial, fungal, viral, and parasitic.[149] It was shown that, in patients with CLL who were receiving fludarabine plus prednisolone, infections occurred more often than in those not receiving steroid therapy.[150]

CLL and Peripheral Nervous System Neurologic Manifestations

CLL involvement of the peripheral nervous system (PNS) albeit very rare, can be manifest in a broad myriad of different ways, including cranial nerve palsies, acoustic neuropathy, ophthalmoplegia, femoral neuropathy, and peripheral neuropathy due to leukemic infiltrations of peripheral nerve roots and/or plexus and spinal roots, with or without associated leptomeningeal involvement.[151-153] Derangements in the immune regulation are frequent in CLL, especially autoimmune hemolytic anemia, but nonhematologic autoimmune neuropathies phenomena, such as the chronic inflammatory demyelinating polyradiculoneuropathy, necrotizing vasculitis, and Guillain-Barré syndrome (GBS), and other inflammatory neuromuscular disorders also are associated with CLL and tend to occur even in the early stages of CLL disease.[154-156] Among them, GBS or its variants, such as the Miller-Fisher syndrome or acute pandysautonomia, have been described several times in the context of CLL.[157-160] Although GBS is a postinfectious, immune-mediated disease generally triggered by *Campylobacter jejuni* infection, it is further known that herpes zoster infection, which is frequent among patients with CLL, significantly increases the risk for developing GBS, and this explains, in part, the many cases of CLL-associated GBS.[161] Myasthenia gravis, an autoimmune disease of the neuromuscular junction was described over a dozen times concurrently with CLL. It is known that the incidence of CLL is higher in patients with myasthenia gravis who have an intact thymus compared with those who have had a thymectomy. However, the exact relationship between both entities remains to be elucidated, that is, if both have a common pathogenesis or their coexistence can be purely coincidental.[162] Regarding the CLL-associated peripheral neuropathies, it is very difficult to guarantee with absolute certainty, even with the aid of clinical and histopathologic data, if their natures are exclusively neoplastic, paraneoplastic, inflammatory, iatrogenic, or incidental. Most probably, in some cases, different etiopathogenic mechanisms take part in the genesis of the neurologic disease.[163]

CLL and Metabolic Neurologic Disease

CLL-associated vitamin deficiencies have been reported in some studies (thiamine, folic acid, cobalamin, tocopherol, and 1,25-dihydroxyvitamin D).[164-168] The proposed hypothesis for the etiopathogenesis of vitamin imbalances found in CLL is related to an increased nutrient consumption by the tumor cells. In patients with CLL, these derangements may go unnoticed but can potentially progress to relevant neurologic disease. CLL-associated thiamine (vitamin B1) deficiency manifestations are generally subclinical.[164] However, under precipitating factors, for example, chemotherapy, continuous vitamin depletion may eventually trigger clinical nervous system manifestations (dry beriberi).

Disturbances in electrolyte equilibrium are uncommon in CLL and are related to the disease process itself or to therapeutic interventions. Among the possible ionic imbalances, hypercalcemia and hyponatremia constitute the most important ones, because life-threatening neurologic derangements may develop. High serum calcium levels in CLL can appear during disease progression (elevation of white blood counts).[169] The mechanisms that underlie hypercalcemia in CLL are related to humoral-mediated bone liberation of calcium by the parathyroid hormone due to parathyroid hormone–related protein produced by the malignant B lymphocytes.[170-175] Hypercalcemia-induced neurologic symptoms include alteration of mental status, lethargy, depression, headache, confusion, and eventually coma. Hyponatremia is another condition that, if left untreated, is fatal due to manifestations of cerebral edema, including headache, confusion, epilepsy, and coma. Coexisting hyponatremia and CLL have been reported in 5 patients, 1 due to iatrogenic causes, in a patient treated with alternative medicine, and the remaining 3 cases in patients with the syndrome of inappropriate secretion of antidiuretic hormone secondary to leukemic meningitis infiltration or pituitary gland invasion.[15,33,44,176] Although very rare, CLL-related electrolyte imbalances should be sought and identified because prompt treatment avoids evolution to clinical manifestations.

CLL and Paraneoplastic Neurologic Syndromes

Paraneoplastic neurologic syndromes are a group of rare disorders that involve any part of the central and peripheral nervous system, the neuromuscular junction, or muscles, and that affect <1% of cancer patients. Paraneoplastic neurologic syndromes are mostly encountered in small-cell lung cancer followed by ovarian and breast cancer, thymoma, and, in a minority of cases, lymphomas.[177,178] As a general rule, the neurologic manifestations precede the clinical onset of cancer and, therefore, can go unnoticed. The recent observations that paraneoplastic neurologic syndromes are, in many instances, immune-mediated disorders led to the increasing importance given to the onconeural antibodies, which recognize antigens expressed by the nervous system and by neoplastic cells as a key means to diagnose true paraneoplastic neurologic syndromes.[179] The spectrum of entities that encompass the paraneoplastic neurologic syndromes can be split into 2 groups. First, the "classic syndromes" are often associated with cancer, whose diagnosis should not delay the search for an occult neoplasm. These syndromes include encephalomyelitis, limbic encephalitis, subacute cerebellar degeneration, subacute sensory neuronopathy, Lambert-Eaton myasthenic syndrome, and opsoclonus-myoclonus. Second, the remaining other disorders, GBS, Stiff person syndrome, subacute sensorimotor neuropathy, and so forth, are defined as "nonclassic syndromes."[180] To date, no association between CLL and paraneoplastic neurologic syndromes has been described. However, there is 1 report that describes a patient with CLL who, after chemotherapy, developed nonhemic autoimmune complications, which included glomerulonephritis, paraneoplastic pemphigus, and neurologic symptoms, with image-documented cerebral lesions suggestive of "nonclassic" paraneoplastic neurologic syndromes. Although this could have been the first report of a possible paraneoplastic neurologic syndrome associated with CLL, ultimately it failed to fulfill the diagnostic criteria of paraneoplastic neurologic syndromes because no onconeural antibodies were detected, and the period of time between CLL diagnosis and the onset of neurologic symptoms exceeded the time limit set out in the criteria.[181] Other entities, previously considered as paraneoplastic neurologic syndromes but no longer in the current recommendations, such as cancer-associated retinopathy and myasthenia gravis, have been associated with CLL and are described elsewhere in this review. However, as mentioned before, the "nonclassic" paraneoplastic neurologic syndromes GBS also was described in association with CLL. However, it was clearly demonstrated that it was not linked to the cancer but to concurrent CLL-related opportunistic infections or an incidental finding.

Conclusions

CNS and PNS complications are important issues that clinicians and hemato-oncologists must bear in mind when dealing with patients with CLL who present with neurologic symptoms. It is necessary to consider neoplastic parenchymal and/or meningeal infiltration; secondary brain tumors; opportunistic infections, including progressive multifocal leukoencephalopathy; CNS hemorrhage; and peripheral neuropathies in the differential diagnosis in these situations. Early identification and prompt CNS-directed treatment or modification of the previous disease management strategy can positively affect morbidity and quality of life. Notwithstanding, a search for prognostic factors for the risk of CNS involvement as well as defining the optimal treatment is needed to achieve a better and durable response and outcome.

Disclosure

The author has stated that he has no conflicts of interest.

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